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Preoperative Anaplastic Glioma Tumor Volume Effects on Patient Survival

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Background and Objectives: The relationship between preoperative tumor volume and patient survival has long been studied, but the results have been inconsistent. Since geometric measurement of tumor volume was used in these studies, the aim of this study was to ascertain whether the inconsistency of the study results is due to less accurate geometric measurement.

Methods: Prognostic tumor volume effects were compared between the planimetry method and the geometric method using survival analysis, performed for 99 patients diagnosed with anaplastic glioma tumor.

Results: A significant correlation was found between planimetry tumor volume and patient survival, but there was no correlation between geometric tumor volume and patient survival. The larger planimetry tumor volume was significantly associated with shorter survival.

Conclusions: The study indicated that in brain tumor research the preoperative tumor volume measured by the geometric method may not be prognostically important. The more accurate measurement, i.e., the planimetry method (based on either computed tomography or magnetic resonance imaging), is needed in brain tumor clinical research and prognostic diagnosis.

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KEY WORDS: planimetry method; geometric method; magnetic resonance imaging; computed tomography; Weibull distribution; exponential distribution; Cox proportional hazards; Kaplan Meier; confounding factors

INTRODUCTION

In the early 1950s, the effect of tumor volume on clinical significance was not recognized. In 1954, Franks [1] found a 38% incidence of prostate cancer in Great Britain that caused only 1.4% of all deaths in men >50 years of age. This suggested that there were 2 forms of cancer: a latent form and a clinically significant form that causes death. However, at that time, the importance of cancer volume as a measure of tumor progression was not recognized. During the last decades, clinical cancer studies have shown that if cancers acquire the capacity to metastasize only as a function of the passage of time and increasing volume, an early small tumor might not behave aggressively. For example, Stamey et al. [2] studied 55 prostate cancers in 139 samples. They found that tumor volume was compatible with clinical outcome. In their results, only cancer volumes of $\geq$0.5 ml probably were significant. Tumors below this value could be regarded as latent in the practical sense. Furthermore, in clinical prostate cancer treated by radical prostatectomy, they found that the frequency of lymph node metastases was linked closely to the cancer volume. The important concept of tumor progression then included the concepts that small tumors were incapable of metastases, the prob-

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ability of metastasis increased with mass doublings (volume), and the mitoses that accompany the increase in volume generate heterogeneity in the new tumor cells, which ultimately cross the threshold for metastases [2]. In brain tumor research, however, the importance of tumor size has long been debated. For example, Reeves and Marks [3] studied 32 patients with glioblastoma multiforme. They found no significant relationship between lesion size and survival.

The earlier quantitative technique for tumor size evaluation was direct measurement of maximal length and width [4]. This led to estimating volume using a spherical or ellipsoid model. With improvements in the technology of image acquisition, several methods of quantifying tumor volume have evolved. In 1988, Albright and Fram [5,6] studied a microcomputer-based technique for 3-dimensional (3-D) reconstruction and volume measurement of computed tomographic (CT) and magnetic resonance imaging (MRI) results in brain tumors. The microcomputer-based planimetry method accurately quantified volumes from CT and MRI scans of irregularly shaped objects and displayed 3-D reconstructions. The planimetry method was demonstrated to be significantly more accurate than spherical, ellipsoid, or rectangular geometric models in quantifying object volume. Although geometric measurement is not accurate for absolute tumor volume, it is adequate for use in comparing relative size of different scans from the same patient and between patients. However, to determine the prognostic importance of tumor volume, the less accurate geometric tumor volume might lead to inconsistent study results. The purpose of this study was to ascertain whether the inconsistency of results is due to use of the less accurate geometric method of tumor volume measurement. This is a retrospective analysis of 99 adults with histologically proven brain tumor.

MATERIALS AND METHODS

Measurements of Tumor Volume

The planimetry method was feasible in both CT and MRI studies. The study we present here was based on the CT image technique. Several methods were used to quantify tumor volume: (1) spherical geometric measurement, volume $= 4/3\ \pi\ r^3$, where r is the radius of the maximum cross-sectional area on the CT image; (2) ABC ellipsoid measurement, volume $= 4/3\ \pi\ ABC$, where A is the tumor's maximum cross sectional diameter, B is the maximal perpendicular diameter to A, and C is the number of CT scans (slices) containing the object; (3) planimetry measurement, volume = (software PC3D). The software PC3D produced 3-D reconstructions and volume quantification based on planimetry tracings of any serial sectioned material [5,6].

Table I summarizes the results of 99 patients with tumor volumes measured by both planimetry and geometric methods. Tumor volumes measured by these 2 methods were very similar; most tumors were ≤ 60 cm^3. Median locations fell in the range 30–45 cm^3 (Table II). A scatter plot (Fig. 1) with an associated linear regression line depicted the relationships between the quantitative preoperative planimetry tumor volume and the geometric tumor volume. The findings indicate that there was a

TABLE I. Characteristics of Patients

Characteristic	No. of patients	Survival (months), median	Age (years), mean
Age (years)			
25–44	12	16.3	
45–65	44	9.8	
>65	43	4.9	
Histology			
Anaplastic astrocytoma	20	13.2	52.5
Glioblastoma multiforme	79	7.2	62.2
Surgery			
Resection	41	9.6	59.3
Stereotactic	58	6.0	60.9
Chemotherapy			
No	41	3.5	65.8
Yes	58	11.5	56.3
Radiation			
No	13	0.9	64.7
Yes	86	9.1	59.6
Hemisphere (lateralization)			
Right side	51	6.5	60.8
Left side	48	8.4	59.7
Bilateral	0		
Lobe			
Frontal	24	12.6	55.9
Parietal	31	5.0	62.9
Temporal	35	7.3	61.1
Thalamus	9	3.8	59.4
Karnofsky score (10–100)			
10–40	15	2.5	64.7
50–60	28	5.4	63.4
70–80	42	9.1	58.4
90–100	14	13.2	54.6

TABLE II. Summary of Preoperative Tumor Volume Measurements

	No. of patients	
Tumor volume (cm^3)	Planimetry measurement	Geometric measurement
0–15	21	26
>15–30	25	19
>30–45	12	14
>45–60	8	10
>60–75	4	8
>75–90	16	4
>90–105	4	7
>105–120	4	4
>120–135	4	3
>135–150	0	2
>150	1	2

direct, highly correlated relationship ($r = 0.945$) between the planimetry and geometric measurements and that the geometric tumor volume slightly overestimated the planimetry tumor volume (regression slope = 1.035). However, in the study of Albright and Fram [5,6], the overestimation rate was higher (regression slope = 1.8).

Patients

One hundred four patients with anaplastic astrocytoma (AA) or glioblastoma multiforme (GBM) were selected for this study. Since 5 patients had missing measurements in either the geometric or planimetry method, only 99 patients were included in the study. These patients were treated from January 1980 to January 1991 at 3 medical centers: Duke University Medical Center, University of North Carolina at Chapel Hill Medical Center, and Durham, North Carolina Veterans Administration Medical Center. Among these patients, 51 were male and 48 were female. A surgical tissue diagnosis had been performed in all patients. Forty-one patients had undergone an open biopsy followed by maximum feasible tumor resection. Fifty-eight patients received stereotactic biopsies. Dates of diagnosis and death (or last known status) were recorded for all patients. The end point of this study was the period of survival. Survival was measured from the date of definitive surgical diagnosis to date of death.

The following factors were recorded: age at diagnosis, tumor histology, duration of preoperative symptoms, tumor lateralization, tumor location, extent of surgery, chemotherapy, radiation therapy, preoperative Karnofsky performance score, and preoperative total tumor volume. Tumors were recorded as right-sided (R), left-sided (L), or bilateral (B). Tumor location was considered to be the lobe in which the tumor was predominantly located: frontal (F), temporal (T), parietal (P), occipital (O), or thalamus (TH). The extent of surgery was recorded from the operative notes. Categories included stereotactic biopsy and resection. No simple biopsy was performed.

Table I gives the characteristics of the patients. Two patients were lost to follow-up. The average age of patients was 60.3 years (range 25–80). Median survival time was 8.1 months. Each patient had 2 preoperative total tumor volume measurements: geometric measurement (denoted ABC) and planimetry measurement (denoted TTV) (Table II). Tumor regions were defined by CT abnormalities. Total tumor volume pertained to the entire region of abnormal CT enhancement, including the intratumor low-density (core) volume that frequently was seen within the region of enhancement. Enhanced tumor volume was determined as the difference between the total tumor and the core volumes.

Table I shows that patients with tumor in the frontal lobes lived longer than patients with tumor in the thalamus lobes. Age was inversely related to length of survival: younger patients lived longer than older patients. Age also had an inverse linear relationship with the preoperative Karnofsky score: younger patients had higher Karnofsky scores than older patients. The preoperative Karnofsky score manifested a linear correlation with length of survival: patients with higher Karnofsky scores lived longer than did those with lower Karnofsky scores. Patients with AA lived nearly 2 times longer than those with GBM. Patients with resection (subtotal or total) surgery lived longer than those with stereotactic biopsy. Radiation therapy had a marked effect on patient survival: patients receiving radiation therapy lived 9 times longer than those without it. Patients receiving chemotherapy lived nearly 3 times longer than those without it.

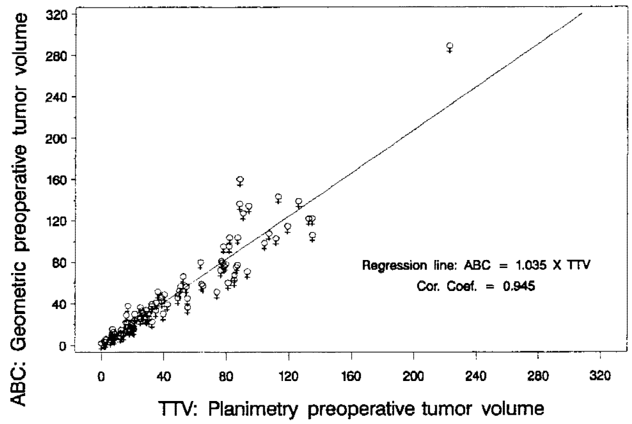

Fig. 1. Correlation between planimetry tumor volume and geometric tumor volume, preoperative data.

Method 1: Prognostic Stratification

To evaluate the tumor volume effect on patient survival, patients were divided into 2 subgroups: those with a large tumor volume and those with a small tumor volume. For the geometric method, 1 subgroup had a tumor volume (ABC) $\leq$34 cm^3 and the other subgroup had a tumor volume (ABC) >34 cm^3. The cut-off point of 34 cm^3 was chosen so that the 2 subgroups had a similar sample size. For the planimetry method, 1 subgroup had a tumor volume (TTV) $\leq$32 cm^3 and the other subgroup had a tumor volume (TTV) >32 cm^3. The cut-off point of 32 cm^3 was also determined so that both subgroups had a similar sample size. Having an equal sample size between 2 subgroups will give the most power in statistical inference.

To remove or reduce the effect of prognostic heterogeneity (i.e., confounding effects or modifier effects), patients were stratified according to similar prognostic expectations. Survival time was then compared between patients of the same prognostic stratum. The advantage of prognostic stratification avoids false-positive or false-negative results and improves efficiency of comparison.

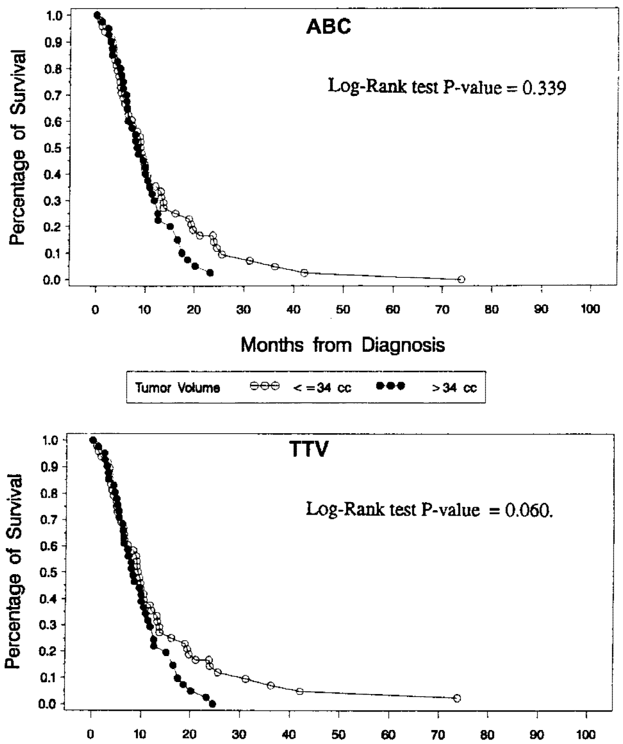

Fig. 2. Survival analysis with preoperative total tumor volume >34 vs. ≤34 cm^3. These patients received radiation. Top: Geometric method (ABC). Bottom: Planimetry method (TTV).

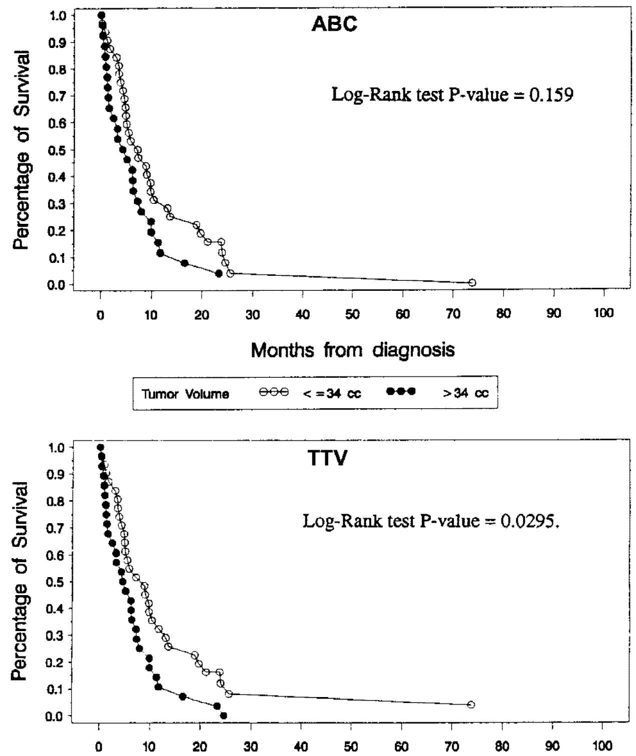

Fig. 3. Survival analysis with preoperative total tumor volume >34 vs. ≤34 cm^3. These patients had stereotactic surgery. Top: Geometric method (ABC). Bottom: Planimetry method (TTV).

Stratified variables. The following prognostic variables were stratified: radiation treatment status (yes or no), extent of surgery (resection or stereotactic), chemotherapy status (yes or no), and preoperative Karnofsky score (≤60 or >60). In each stratum, the relationship between tumor volume and survival was analyzed by the log-rank test. The survival curve of time to death was estimated by the Kaplan-Meier method. The survival analysis results in the radiation = yes stratum are shown in Figure 2. For the radiation = no stratum, since neither method (planimetry or geometry) explored a significant survival difference between 2 subgroups, the result is not presented. The survival analysis results in the surgery = resection stratum are shown in Figure 3. For the surgery = stereotactic stratum, neither method (planimetry or geometry) explored a significant survival difference between 2 subgroups, and therefore, the result is not presented. The survival analysis results in the chemotherapy = yes stratum are shown in Figure 4. For the chemotherapy = no stratum, neither method (planimetry or geometry) explored a significant survival difference between 2 subgroups, so the result is not presented. The survival analysis results in the Karnofsky score ≤60 stratum are shown in Figure 5. Since for the Karnofsky score >60 stratum, neither method (planimetry or geometry) identified a survival difference between 2 subgroups, the result is not presented.

Results. For the radiation = yes stratum, patients with a small tumor volume lived moderately longer than those with a large tumor volume by the planimetry method ($P = 0.06$). However, the geometric method did not explore the survival difference between the 2 tumor volume subgroups ($P = 0.339$). For the surgery = stereotactic stratum, the subgroup of patients with small tumor volumes lived significantly longer than those with large tumor volumes by the planimetry method ($P = 0.0295$). However, the geometric method did not explore the survival difference ($P = 0.159$) between the 2 subgroups. For the chemotherapy = yes stratum, patients with a small tumor volume lived significantly longer than those with a large tumor volume by the planimetry method ($P = 0.033$). The geometric method also explored the survival difference between the 2 subgroups ($P = 0.035$). For the Karnofsky score ≤60 stratum, patients with a small tumor volume lived significantly longer than those with a large tumor volume by the planimetry method ($P = 0.011$). However, the geometric method did not explore the survival difference ($P = 0.175$) between patients with a small tumor volume and patients with a large tumor volume.

The stratified analysis revealed that the planimetry method showed significant survival differences between the 2 tumor volume subgroups, whereas the geometric method did not show a survival difference between the 2

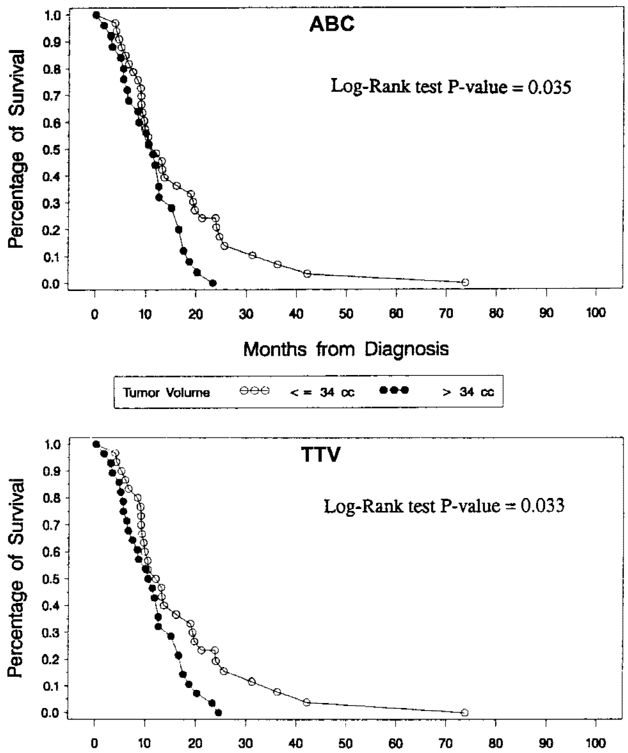

Fig. 4. Survival analysis with preoperative total tumor volume >34 vs. ≤34 cm^3. These patients had chemotherapy. Top: Geometric method (ABC). Bottom: Planimetry method (TTV).

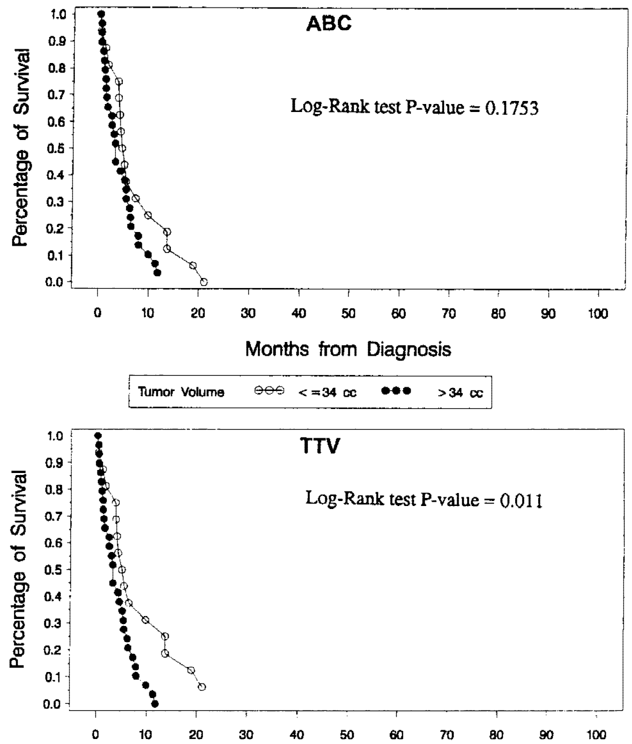

Fig. 5. Survival analysis with preoperative total tumor volume >34 vs. ≤34 cm^3. These patients had a Karnofsky score ≤60. Top: Geometric method (ABC). Bottom: Planimetry method (TTV).

subgroups for most strata. We had conducted a similar analysis of postoperative data for the same patients. A summary of log-rank tests for pre- and postoperative tumor volume data is presented in Table III. A significant correlation was found between planimetric tumor volume and survival for both pre- and postoperative data, but there was no correlation between geometric tumor volume and survival in most strata for both pre- and postoperative data. These results coincided with the studies in publications [4,7]. In the meantime, we noticed that with the planimetry method the *P* values from the postoperative data were much smaller than those from the preoperative data, which indicated that the postoperative tumor volume was of more prognostic importance than the preoperative tumor volume.

Method 2: Parametric Models

Stratification as a technique to control confounding has a number of advantages. It is easy to carry out and allows both investigators and readers to achieve a clear understanding of the interrelationships among the exposure, disease, and additional confounding variables. A fundamental problem with the stratified analysis is its inability to control simultaneously for even a moderate number of potential confounders. Even with a relatively large study, it is very likely that many of these strata would contain few if any individuals, making analysis unreliable or even impossible. Multivariate analysis allows for efficient estimation of measures of association while controlling for a number of confounding factors simultaneously. For the parametric model, the form of the true population survival distributional function was almost always unknown, and many distributional forms had been used for describing failure time data.

TABLE III. Log-Rank Tests for Survival Difference between Tumor Volume Subgroups for Pre- and Postoperative Data

	P, planimetry		*P*, geometry	
Stratification	Pre-operative	Post-operative	Pre-operative	Post-operative
Radiation = yes	0.06	0.039	0.339	0.215
Surgery = stereo	0.030	0.0039	0.159	0.042
Karnofsky ≤60	0.011	0.0036	0.175	0.075

We consider 2 popular parametric survival distributions: the exponential and Weibull distributions. The exponential distribution is often used to model events that occur "at random in time" [8]. It has the property that the future lifetime of a subject is the same, no matter how "old" the subject is. This "ageless" property also makes exponential distribution a poor choice for modeling human survival except over short periods. The Weibull distribution is a generalization of the exponential distribution; it does not assume a constant hazard rate and has

TABLE IV. Results of Parametric Analysis

Multivariate model	*P*, planimetry	*P*, geometry
Model 1		
Age	0.0001	0.0001
Radiation (yes or no)	0.0001	0.0001
Surgery (resection or stereotactic)	0.187	0.335
Tumor volume	0.009	0.124
Model 2		
Age	0.0003	0.0001
Radiation (yes or no)	0.0001	0.0001
Chemo (yes or no)	0.09	0.118
Tumor volume	0.018	0.183
Model 3		
Age	0.0009	0.001
Radiation (yes or no)	0.0001	0.0001
Histology (AA or GBM)[a]	0.058	0.03
Tumor volume	0.09	0.331
Model 4		
Age	0.0005	0.0002
Radiation (yes or no)	0.0001	0.0001
Karnofsky score	0.021	0.018
Tumor volume	0.040	0.308

[a]AA, anaplastic astrocytoma; GBM, glioblastoma multiforme.

broader applications. Therefore, the Weibull distribution was employed as an underlying distribution in our brain tumor study. Since age and radiation were important confounding and modifier variables, they were kept in the parametric models. The results of the Weibull analysis are shown in Table IV.

Results. The preoperative tumor volume measured by the planimetry method was an important prognostic factor ($P < 0.1$) in all 4 models, while the preoperative tumor volume measured by the geometric method was not a significant factor in the 4 models. We noticed that in the chemo = yes stratum of the previous section, geometric tumor volume was a prognostically important factor ($P = 0.035$) but after adjusting for more factors in the parametric model it was no longer important ($P = 0.183$).

Method 3: Overall Models

The previous multivariate analysis confirmed that age, histology, and radiation treatment were prognostically important or moderately important factors by both planimetry and geometric methods ($P < 0.1$). Tumor volume was also an important factor in determining survival by the planimetry method, but it was not an important factor by the geometric method.

We investigated the tumor volume effect on survival using the overall models. The overall models consisted of the most possible survival-related factors. Factors such as sex, blood type, height, and weight had the least influence on survival time. They were not included in the overall models. Since Karnofsky score was highly correlated with age (Table I), it was also not included in the overall models. The clinical variables involved in the overall models were as follows: age at diagnosis, duration of preoperative symptoms (months), location of tumor in lobe (F, T, P, O, TH), histology of tumor (AA, GBM), radiation treatment (yes, no), chemotherapy treatment (yes, no), extent of surgery (resection, stereo), location of hemisphere with tumor (R, L, B), preoperative tumor volume by geometric method (ABC, cm^3), and preoperative tumor volume by planimetry method (TTV, cm^3). The overall multivariate analysis was performed on 99 patients. The survival model was as follows: survival = age + histology + chemotherapy + surgery + radiation + duration of symptom + lobe + hemisphere + tumor size.

TABLE V. Results of Overall Multivariate Models

	Planimetry method, *P*		Geometric method, *P*	
Variables	Weibull	Cox PH[a]	Weibull	Cox PH[a]
Age	0.0064	0.013	0.0069	0.027
Histology	0.0086	0.045	0.004	0.025
Surgery	0.369	0.310	0.392	0.350
Chemotherapy	0.0086	0.0009	0.007	0.0008
Radiation	0.0001	0.0001	0.0001	0.0001
Duration of symptom	0.076	0.365	0.083	0.343
Lobes	0.086	0.045	0.119	0.067
Hemisphere	0.118	0.136	0.140	0.153
Geometric method	—	—	0.233	0.188
Planimetry method	0.027	0.037	—	—

[a]PH, proportional hazards.

To compare the 2 tumor volume measurements, the model was fitted by the geometric and planimetry tumor volumes, respectively. Since the Cox proportional hazards (Cox PH) model is very popular for the analysis of survival data, the overall models were analyzed by both the Weibull and Cox PH analyses. The results are presented in Table V.

For the geometric method, the tumor volume variable ABC was included in the overall model; for the planimetry method, the tumor volume variable TTV was included in the overall model. The overall model using the geometric method was designated the geometric model and that using the planimetry method, the planimetry model.

Results. The results from both the Weibull and the Cox PH analyses were quite similar except for duration of symptoms. In the Weibull analysis, the *P* value (near 0.08) for the duration of symptoms was much smaller than that (near 0.30) in the Cox PH analysis. A residual plot from the Cox PH analysis manifested somewhat of a violation from the proportion assumption, which indicated that this analysis may not be appropriate for this study. Further adjustment of the Cox PH model is needed.

Chemotherapy, radiation therapy, histology, and age

were prognostically important factors in both models. Patients with AA lived significantly longer than those with GBM. Patients who underwent chemotherapy and radiotherapy lived longer than those without these treatments. Younger patients lived longer than older patients.

Preoperative tumor volume measured by the planimetry method was an important prognostic factor in the planimetry model. Patients with a small preoperative tumor lived longer than those with a large preoperative tumor. Tumor volume was not a significant factor in the geometric model.

The lobe factor was moderately important in the planimetry model: patients with tumor in the frontal lobes lived longer than those with tumor in the thalamus or parietal lobes. However, the lobe was not important in the geometric model.

Since these are the non-nested models, it is somewhat difficult to compare the goodness of fit between them.

DISCUSSION

In 1988, Wood et al. [7] studied the relationship between tumor size and patient survival with both pre- and postoperative data using the geometric method. They found that the preoperative tumor area was unrelated to survival ($P = 0.48$) but the postoperative tumor area was an important prognostic factor ($P < 0.0001$). The smaller the residual tumor, the longer the patient lived. Reeves and Marks [3] also studied the prognostic significance of preoperative lesion size for GBM. The results showed a lack of correlation between the geometric lesion size and prognosis in GBM among 32 patients who underwent surgery followed by irradiation. The possible reasons for the lack of correlation between the preoperative tumor volume and survival were (1) that there may be very rapid tumor growth immediately prior to presentation, (2) the location of a lesion at presentation may be more important than tumor size, and (3) certain factors, such as age, histology, Karnofsky score, and treatment used, may sufficiently outweigh the significance of lesion size. With the improvement of imaging techniques, another critical point is that the less accurate geometric tumor measurements in the early studies would cause inconsistent and less reliable results.

Since the planimetry measurement was more accurate than the geometric measurement in our study, we showed that the accurate measurement of tumor volume played a critical role in the evaluation of the statistical significance of tumor volume on survival. In method 2, after we stratified prognostic factors such as Karnofsky score, radiation therapy, chemotherapy, and surgery status, the preoperative tumor volume measured by planimetry was statistically significant. Meanwhile, for most strata, the geometric tumor volume was not a significant factor. The parametric model also indicates that the preoperative tumor volume measured by planimetry is an important prognostic factor after adjustments for more factors in the analysis but that the preoperative tumor volume measured by the geometric method is not a significant prognostic factor. The overall multivariate analysis, after adjustment for the most important factors, showed that the preoperative tumor volume measured by the planimetry method was again a significant prognostic factor but that the geometric tumor volume was not.

In conclusion, this study confirms that in cancer clinical research, particularly in brain tumor research, the preoperative tumor volume measured by the geometric method may not be prognostically important. The more accurate measurement (i.e., the planimetry method) is needed in brain tumor clinical research and in prognostic diagnosis. The relationships between tumor volumes of other types of cancer and survival deserve further prospective investigation.

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